THE HUXLEY LECTURE ON RECENT STUDIES OF IMMUNITY, WITH SPECIAL REFERENCE TO THEIR BEARING ON PATHOLOGY.*

GENTLEMEN,—You will readily believe that with my deep appreciation of the high honor conferred by the invitation to deliver the fourth Huxley lecture there was joined a sense of great embarrassment in being called upon to follow in this office three such leaders of world-wide fame as Sir Michael Foster, Professor Virchow and Lord Lister. But the letter of the Committee of the Charing Cross Hospital Medical School stated that the choice of a successor to these great names was 'a tribute of our admiration for the great army of scientific workers on the other side of the Atlantic.' While I cannot assume to occupy any other place in this army than that of a soldier in the ranks, I felt that if my acceptance of this invitation could be regarded as in any sense an expression of appreciation by American workers in science of the commendation and good-will of our British colleagues, of our large indebtednesss to them, of our sense of the common interests, the comradeship and the kinship of the English-speaking peoples on both sides of the ocean, I should not decline, even if summoned to occupy a position of danger.

There was another consideration which I may be permitted here to mention. Through Huxley there is, if not a bond, at least a link, between the Charing Cross Hospital Medical School and the Johns Hopkins University. This lectureship was founded to commemorate the fact that Huxley received his entire medical education at the Charing Cross Hospital Medical School. While throughout America the name of Huxley is held in high honor as that of a great discoverer and interpreter in science, and while the influence which he has exerted upon popular as well as scientific opinion through those messages peculiarly fitted to the needs of English thought is not less there than among his own countrymen, we at the Johns Hopkins University have special reasons to acknowledge our gratitude to him. He crossed the ocean to deliver the principal address at the opening of this University in 1876, and he then gave utterance to ideas concerning university, and especially medical, education which were at the time and have remained an inspiration and a guide to us. Then, too, the Johns Hopkins University owes to Huxley and to Michael Foster the accession to its faculty of my lamented colleague, Newell Martin, who by the introduction and development of the biological methods and conceptions of his teachers gave such new directions and so great an impulse to biological study in America that his own work and that of his pupils started for us a new era in this department.

The first Huxley lecturer has made it unnecessary for his successors to dwell upon Huxley's studentship at the Charing Cross Hospital, upon the important influence which this had upon his career, or upon his great services to medical science, although his chief title to fame lies outside of the domain of medicine. I should like, however, to quote a passage, although it must be familiar to you, from Mr. Leonard Huxley's charming 'Life and Letters' of his father, which has appeared since the date of Sir Michael Foster's lecture, for it shows that 'it was at Charing Cross Hospital where Huxley first felt the influence of daily intercourse with a really able teacher.' He says:

> No doubt it was very largely my own fault, but the only instruction from which I obtained the proper effect of education was that which I received from Mr. Wharton Jones, who was the lecturer on physiology at the Charing Cross School of Medicine. The extent and precision of his

* Delivered at the opening of the winter session of Charing Cross Hospital Medical School, on October 1, 1902.

knowledge impressed me greatly, and the severe exactness of his method of lecturing was quite to my taste. I do not know that I have ever felt so much respect for anybody as a teacher before or since.

Wharton Jones, who will doubtless be longest remembered as the discoverer of the amœboid movements of the white blood corpuscles, was an experimental physiologist and pathologist of much originality, and it seems to me that there has not been, even in his own country, so full a recognition of his work as its importance merits.

Before passing to the special theme of this lecture it is fitting that I should pause, if only for a moment, to call to mind with affection and reverence that recently departed great man who honored and delighted you four years ago, and who has conferred such high distinction upon the office of Huxley lecturer. When one considers the full import of the discovery and establishment by Virchow of the principles of cellular pathology, that this constitutes the secure foundation upon which nearly two generations have built and future generations will continue to build the edifice of scientific medicine, I do not know what greater name there is in the whole history of medicine than that of Rudolf Virchow. How noble his character! With what amazing industry, versatility and keenness of intellect did he fruitfully cultivate the new fields which he had opened to research as well as other departments of science! With what devotion and beneficial results did he give his time and abundant knowledge to the service of the public and of our profession! We mourn the loss of a hero of medicine and of science, a benefactor of his race, and we rejoice in the rich fruitage of a long and well-spent life.

The first place in experimental medicine to-day is occupied by the problems of immunity, and, in accordance with the trust of the Huxley lectureship, which provides that the lecture shall relate to 'recent advances in science, and their bearing upon medicine and surgery,' I have chosen for my theme 'Recent Studies of Immunity, with Special Reference to their Bearing on Pathology.' As it would be hopeless to attempt a complete review of this broad subject within the space of a single lecture, I shall dwell more particularly upon certain of its aspects, not always of necessity the most important ones, which I conceive to be less familiar to most physicians, or which have engaged my attention, although much which I shall say is of course known to those who have followed the results of recent work in these new lines of investigation.

Under 'studies of immunity' I have included, as a matter of convenience, though not with strict accuracy, investigations which, although the direct outgrowth of those primarily directed toward a solution of the problems of immunity, have extended far beyond these bounds, and have revealed specific properties of cells and fluids in health and in disease of the broadest biological interest. We find illustrated here the familiar fact, nowhere more important to recognize than in medicine, that the sciences are interdependent, that discovery in one field sheds light in most diverse and often unexpected directions, and opens new paths to research. We shall see also exemplified the fructifying influence upon the advancement of knowledge of the discovery and application of new methods of investigation.

In endeavoring to follow in its intimate workings the contest of the living body with its invaders, the attention of investigators has naturally been drawn both to the action of the cells and to the properties of the fluids of the body in this struggle, to the latter sometimes without sufficient

consideration of the dependence of the humors in their composition upon the cells. Each of these lines of study, whether followed separately or conjointly, has led to the discovery of important facts relating to the mechanism of immunity.

We owe to Metchnikoff and his pupils the most important observations concerning the direct participation of leucocytes and other cells in the processes of infection and the production of immunity. Whatever attitude one may take toward Metchnikoff's well-known phagocytic theory of immunity, one must recognize the wealth of new facts which he has brought to light, and must admire the skill and fertility of resource with which for two decades he has defended this theory against severe assaults, and he has done so, in my judgment, with a large measure of success. With wonderful ingenuity in his recent book on immunity he rescues the phagocytes and applies to a deeper insight into their activities results of his opponents' work.

The other line of research, in some respects more important, was opened by Nuttall in 1888, working in Flügge's laboratory, by his systematic study of the antibacterial properties of the body fluids, particularly of the blood serum. It is true that there were previous indications of the power of fresh blood to kill bacteria; indeed, if one wishes to trace this matter historically to its roots he must go back to John Hunter, who was quite familiar with the antiputrefactive power of fresh blood, although of course he knew nothing of bacteria. Hunter showed that putrefying fluid could be added in small quantity to fresh blood without setting up putrefaction; and in elaborating his favorite doctrine of the 'living principle of the blood' he interested himself greatly in certain phenomena which, interpreted in the light of our present knowledge, are clear anticipations of some recent findings.

After Nuttall our knowledge of the bactericidal power of the blood serum was extended by Buchner and others; but the next advance of fundamental importance in this direction was Pfeiffer's discovery in 1894 of the quick extracellular disintegration and solution of cholera spirilla in the peritoneal cavity of immunized guinea-pigs or in that of normal guinea-pigs treated with immune serum, and of the presence in the immune serum of a specific substance concerned in the bacteriolytic process although by itself without bactericidal power.

In the meantime Behring had made his great discovery of antitoxic immunity and of the protective and curative value of antitoxic serum, and Ehrlich had done much to elucidate the nature of this form of immunity. It soon became apparent, however, that immunity from the great majority of bacterial infections does not depend in the main upon the antitoxic principle. The attention of bacteriologists, therefore, was drawn more and more to the so-called 'Pfeiffer phenomenon,' which was found to be of great general significance; and starting from this, and especially from the investigation of the analogous and much more readily studied solution of red corpuscles by foreign serum, there has followed in rapid succession up to the present time a series of new and most interesting discoveries and conceptions with which are connected many names, but most prominently those of Metchnikoff and Bordet, and of Ehrlich and Morgenroth.

Through these various studies of immunity we have become acquainted with an important physiological capacity of the healthy organism, the extent, and in most instances the existence, of which was unsuspected until quite recent years. This capacity is the power to produce substances specifically antagonistic to all sorts of foreign cells and cellular products and de-

rivatives. The substances capable of inducing this immunizing reaction appear to be mainly of an assimilable, albuminous nature, or at least intimately associated with such material, although it has been proved that certain non-albuminous derivatives of proteids have the same power.* The mode of antagonism of the specific bodies formed in response to the reception within the living organism of substances capable of inducing the necessary reaction varies with the nature of these latter substances, and consists in such diverse manifestations as neutralization of poisons and of ferments, injury or destruction of cells, associated with characteristic morphological changes, cessation of motility of cells or their appendages, agglutination of cells, precipitation, and coagulation. In accordance with these different effects, the corresponding antagonistic bodies, or antibodies, as they are called, are classified as antitoxins, antienzymes, cytotoxins, agglutinins, precipitins and coagulins, and even against these bodies, with the exception of the antitoxins, antagonists have in turn been produced. All of these bodies are in varying, but usually high, degree specific with reference both to the nature and to the source of the material upon which they exert their characteristic effects.

The cytotoxins or cytolysins include not only the bacteriolysins and hæmolysins, but also a great number of other cellular toxins present in the sera of animals which have received injections of cells from a different species. To every cellular group of an animal species there appears to correspond a specific cytotoxin. To designate these various cytotoxins such self-explanatory names as leucotoxin, spermotoxin, nephrotoxin, neurotoxin, thyreotoxin, syncytiotoxin are used. Their specificity extends not only to the nature of the cells, but also to the species of animal furnishing the cells used for their production.

One of the most important results of recent work is the separation of these specific antibodies into two groups, in one of which, represented by the antitoxins, the antagonists are single bodies; while in the other, represented by the cytolysins, the antagonistic effect requires the cooperation of two bodies. Of these two bodies the one which actually destroys the foreign cells, or induces other specific effect, is normally present in the cells or fluids of the organism, but it seems incapable of action without the intermediation of a body which is distinguished from it by greater resistance to heat, and which is produced by the immunizing reaction, although it may also be normally present in smaller amount.* The two elements composing a cytolysin exist quite independently of each other, so that one may be present without the other, or be artificially removed without affecting the other. Of the multitude of names proposed for these cytolytic components those most commonly used for the body which is the specific product of immunization, although it may also exist normally,

* Specific precipitins have been produced by injection of crystalline and other so-called pure proteids. Obermayer and Pick produced immune bodies by the use of non-albuminous products of tryptic digestion of certain albumins. Jacoby has shown that the specific body concerned in ricin immunization is non-albuminous. A. Klein obtained entirely negative results with injections of starch, glycogen, glucose, gum arabic and gelatine.

* Metchnikoff believes that the complement or cytase, which in his opinion exists under normal conditions solely within cells, not free in the plasma, acts in natural immunity without the cooperation of an intermediary body or fixative, the latter being concerned only in acquired or artificial immunity. The evidence seems, however, to favor the view that in this regard the conditions are similar in both forms of immunity, the main difference being the presence of a much larger amount of the specific immune body in the latter.

are intermediary body, immune body, amboceptor, sensitizer, fixative, preparative, desmon, and for the other body complement, alexin, cytase. It is this latter body which contains the atomic group described as toxophoric or zymophoric.

Concerning the source, mode of action and constitution of the specific antagonistic bodies we are very imperfectly informed. That they are of cellular origin seems certain, and Ehrlich with great ingenuity, on the basis of a brilliant series of experiments, has advanced a hypothesis regarding them which, in my opinion, better than any other hitherto suggested, accords with the known facts, and in promoting discovery has already done the greatest service of which a working hypothesis is capable. Ehrlich has so recently and so fully in the Croonian lecture presented before English readers his hypothesis of the side chains or receptors and the basis for it, that I need only recall to your minds his conception that the toxins, cells and other substances which lead within the living body to the production of antitoxins, cytolysins and other antagonists have this capacity only through the possession of specific affinities, called haptophore groups, for corresponding haptophore groups belonging to side chains or receptors of certain cellular constituents of the body, and that in consequence of this appropriation of receptors, others of like nature are reproduced in excess of the needs of the cell, and these being shed into the lymph and blood, there constitute the antitoxins, intermediary bodies, agglutinins and other specific antagonists. The antitoxic receptor has only a single combining affinity, which is for the toxin, whereas the cast-off receptors constituting the intermediary bodies of cytolysins have at least two affinities (hence called amboceptors by Ehrlich), one of a more highly specialized nature being for the invading bacteria or other foreign cells, and the other for the complement.* The antibody enters quantitatively into definite chemical union with its affinitive substance. The essence of Ehrlich's theory concerning antitoxin is thus tersely expressed by Behring: 'The same substance which, when incorporated in the cells of the living body, is the prerequisite and condition for an intoxication becomes the means of cure when it exists in the circulating blood.' So of the twofold bactericidal and cytolytic agents we may say that the living body possesses substances which may protect it by destruction of invaders or may injure it by destruction of its own cells, according to the mates with which these substances are joined.

An inquiry which naturally arises in this connection is: What is the physiological mechanism called into action in the processes resulting in the production of antitoxins, cytolysins and similar bodies? We have no reason to suppose that the animal body is endowed with properties specially designed to meet pathological emergencies. Its sole weapons of defense, often lamentably imperfect for morbid states, are

* According to Ehrlich's latest conception, resulting from investigations to demonstrate the multiplicity of complements, an amboceptor has a single cytophilic affinity, and a number of complementophilic affinities differing in their avidity for various complements. He regards the agglutinins, precipitins and coagulins as uniceptors of more complex structure than the antitoxins, but Bail has recently brought evidence to show that agglutinins, like cytolysins, are composed of two elements. For the purposes of this lecture, it is not deemed necessary to enter into these or many other details of this complicated subject. For comprehensive and admirable critical reviews of recent theories of immunity and Ehrlich's hypothesis of the receptors, I would refer to Dr. Ritchie's papers in the *Journal of Hygiene*, Vol. II., No. 2, and succeeding numbers; and to Dr. Aschoff's paper in *Zeitschrift f. allgem. Physiologie*, Bd. III., Heft 3.

adapted primarily to physiological uses.* To the foregoing inquiry Ehrlich answers that the mechanism concerned is one physiologically employed for the assimilation by the cells of food. The receptors are in the cells, not for the purpose of linking poisons to the cells but to seize certain food stuffs, particularly the proteids, and the toxins and bacterial and other foreign cellular substances, if capable of inducing the immunizing reaction, chance to have the requisite combining affinities for the food receptors. It is interesting that Metchnikoff also, though from a different point of view, refers the mechanism of immunity to the physiological function of assimilation of food by the cells.

Inasmuch as, according to Ehrlich's hypothesis, the specific antagonistic substances resulting from the injection of toxins and of foreign cells or derivatives of cells exist preformed in cells of the normal body, there would appear to be no reason why any one of them might not occasionally be present normally free in the blood or other fluids. In fact, many of them—such as diphtheria and tetanus antitoxins, various antienzymes, bactericidal, hæmolytic and other cellular toxins, agglutinins and a number of other bodies of this class, as well as their antibodies—have been found repeatedly, though of course in the case of many inconstantly and with marked differences between individuals and species, in the blood of healthy human beings or animals when their presence could not reasonably be attributed to a previous specific immunization. Of these normal antibodies the only one which is increased in amount by the process of immunization is that specifically related to the material used to bring about the reaction. As already stated, it is the intermediary body,* not the complement, which is generated in immunization against bacteria and other cells.

* W. H. Welch, 'Adaptation in Pathological Processes,' *Trans. Congress American Physicians and Surgeons*, 1897, Vol. IV.

The foregoing statements, though of necessity condensed and incomplete, about the general characters of the specific antibodies will, I trust, help to a better understanding of what is to follow concerning the bearing of some of these discoveries on medical science and practice. I realize the difficulties which you must already have experienced, if unfamiliar with these new lines of research, in following a brief presentation of a subject in which not only are the facts so complex, and the ideas so novel, but the terminology so strange and burdened with such a multitude of confusing synonyms. While deploring the multiplication of unnecessary new terms, I should like to quote in this connection a wise remark of Huxley:†

"If we find that the ascertainment of the order of nature is facilitated by using one terminology, or one set of symbols, rather than another, it is our clear duty to use the former; and no harm can accrue so long as we bear in mind that we are dealing merely with terms and symbols."

The most remarkable and characteristic attribute of these antibodies is the specificity of their relation to the substances which have led to their formation. Of some of them, such as diphtheria or tetanus antitoxin, this specificity is nearly absolute; of other, such as the precipitins, it is only relative. This property is the basis of new and most valuable methods for the identification of species and the determination of genetic relations—species not only of living

* I use in this lecture the name 'intermediary body' in preference to the more technical term 'amboceptor,' although Ehrlich applies the German equivalent—*Zwischenkörper*—only to normal as distinguished from immune amboceptors.

† Huxley, 'On the Physical Basis of Life,' 'Collected Essays,' Vol. I., p. 164, New York, 1893.

things, but also of chemical substances and of disease.

The resemblances and the differences thus revealed are doubtless fundamentally of a physico-chemical nature, but in many instances they transcend the powers of the microscope or of ordinary chemical tests to detect.

The results already attained by the method of serum diagnosis*—using this expression in its widest sense—are not only of interest and importance to the biologist, physiologist and chemist, but of great practical value to the bacteriologist and the physician. As this is not an aspect of my subject, broad and important as it is, upon the details of which I propose to dwell, it must suffice to present, by way of illustration, examples of the diagnostic application of different kinds of specific serums.

The only certain means of detecting toxins of the class of diphtheria or tetanus toxin, snake venom and certain vegetable poisons of the same category is their neutralization by the corresponding antitoxic serums. Occasion may arise where such detection is of practical and even medicolegal importance, as has been exemplified in India, where the criminal use of cobra venom is not unknown.

* The general procedure followed in the production of specific serums is the injection into a suitable animal at intervals of time repeated doses of toxins, bacteria, foreign cells, or other material against which the antibody is desired. For example, if a specific precipitating or a hæmolytic serum for human blood is wanted, an animal, say a rabbit, is injected subcutaneously or intraperitoneally at intervals of three or more days with five or six doses of human serum or human red blood corpuscles. At the end of this time the rabbit's serum has acquired the property of precipitating human serum in strong dilutions, or of dissolving human red blood corpuscles, if these were used for the injection. Within limits the less closely related the two species of animals the more powerful is the antagonistic effect of the specific serum. This is true especially in the case of cytotoxic serums.

The application of serum diagnosis which is most familiar to physicians is the agglutinative test for typhoid fever. The principles of the agglutinative reaction were worked out in the laboratory of Professor Gruber in Vienna by himself and Durham, and were there first applied to the diagnosis of typhoid fever by Grünbaum, who was anticipated in his publication by Widal, who has made a thorough clinical study of the subject. The method is of great value, not only in the diagnosis of disease, but also in the identification of bacterial species and the recognition of relationships between species. Durham, to whom we owe important contributions to this subject, has given an ingenious hypothetical explanation of mutual agglutinative reactions, the main features of which are paralleled in Ehrlich and Morgenroth's doctrine, based upon experiments, relating to the multiplicity of cell receptors and of amboceptors concerned in hæmolysis.*

We have found the agglutinative reaction an indispensable aid in the study of the series of cases of paratyphoid fever which have come under observation in Dr. Osler's wards at the Johns Hopkins Hospital, and which otherwise it would have been scarcely possible to have separated from typhoid fever.† The occurrence of paratyphoid fever as a distinct disease affords an explanation of a certain proportion of the failures of the serum from supposed typhoid fever patients to clump typhoid bacilli. Not less valuable is the serum test in the diagnosis of *Bacillus dysenteriæ* Shiga and of the diseases caused by it. This microorganism has been shown by Flexner and his pupils, Vedder and Duval,

* Durham, *Journal of Experimental Medicine*, January 15, 1901, Vol. V., p. 353. Ehrlich and Morgenroth, *Berl. klin. Woch.*, May 27, 1901, p. 570.

† See papers on paratyphoid fever, by Johnston, Hewlett and Longcope in *American Journal of Medical Sciences*, August, 1902.

to be the cause of our acute dysenteries, and recently in Baltimore Duval and Basset, working with the aid of the Rockefeller Institute for Medical Research at the Thomas Wilson Sanitarium for Children, have discovered that this same bacillus is in all probability the specific agent of infection in the summer diarrhœas of infants.

Bacteriolytic serums have been used by Pfeiffer in the differentiation of cholera and allied spirilla, but few other bacteria present equally well the Pfeiffer reaction, which is not nearly so useful or handy a means of identification as the Gruber-Durham reaction.

Of other cytolytic serums the hæmolysins have been by far the most carefully studied. One of the most interesting results of this study has been the determination by precise quantitative methods of resemblances and of differences between red blood corpuscles which in no other way could be distinguished. These resemblances and differences relate to the red corpuscles not only of different species of animals, but also to those of individuals of the same species. Although we constantly assume the existence of cellular differences between individuals and between species, these are for the most part of so subtile a nature as to elude our methods of observation. The exact demonstration of such differences by the use of cytolytic serums is therefore of especial interest. My assistant, Dr. H. T. Marshall, in an unpublished research, conducted under the direction of Professor Ehrlich and Dr. Morgenroth, upon the receptors of the red blood corpuscles of man and of two species of monkey, found that while man and the monkeys each have receptors not shared by the other, they also have a large number of receptors in common.

This result is in harmony with Nuttall's interesting observations on a much more extended scale regarding phylogenetic relationships between animal species, as shown by the reaction of their blood with the specific precipitins discovered by Tchistowitch and Bordet, and introduced into practical medicine by Wassermann. This biological test to determine the source of blood, when used with proper precautions, far surpasses in accuracy all other methods for this end. While it would lead too far from my purpose to follow this subject farther, I cannot in this connection forbear at least mentioning one of the earliest and most suggestive papers on this class of antibodies—that 'On Immunity against Proteids,' by Walter Myers, who gave up his life in the cause of science and of humanity, and whose early death is so great a loss to English medical science.

I shall ask your attention now to some considerations concerning the bearing of recent studies of immunity on the nature and action of toxins. This subject is, of course, of the greatest pathological as well as bacteriological importance, and I believe a closer cooperation than now exists between bacteriologists and pathologists in its study would further the surer and more rapid advancement of our knowledge about it. One misses only too often in purely bacteriological papers on this subject exact knowledge and descriptions of pathological conditions, and, on the other hand, pathologists often fail to utilize pertinent facts and ideas which are familiar to bacteriologists.

The discovery by Roux and Yersin of the diphtheria toxin, the studies by Behring and Kitasato of tetanus toxin leading up to Behring's epochal discovery of antitoxin, and the later investigations of Ehrlich on the constitution of diphtheria toxin and the origin and mode of action of antitoxin are the great events in the most brilliant and securely founded chapter of modern studies of immunity. Through these

researches we became acquainted with a class of poisons secreted by certain bacteria, and present in solution in culture fluids. The evidence is conclusive that these soluble toxins enter, as assimilable substances, into direct combination with constituents of the body cells for which they have an affinity, and only thereby are enabled to bring about immunity or to exert toxic effects. As shown by the modifications of toxins called toxoids, the toxic property may be destroyed without loss of the combining power, and without removal of the immunizing power. According to Ehrlich's helpful conception, based on a large amount of experimental evidence, and now very generally accepted, the combining power of the toxin molecule resides in a group of atoms, designated as the haptophore group, with affinity for the corresponding haptophore groups of the side chains or receptors of cellular constituents, and the toxic power pertains to another and less stable atom complex in the molecule.

By means of these facts, and legitimate deductions from them, we are enabled to explain in a satisfactory way susceptibility to poisoning by these soluble toxins, their selective action upon the cells of the body, and their quick disappearance after injection into the circulating blood. In one infectious disease and in one only, to wit tetanus, are we able to explain the clinical and pathological phenomena in minute detail on the basis of our knowledge of the causative microorganism and its poisonous products. The nearest approach to this instance is diphtheria, but here we have not yet been able to follow the trail of the toxins within the body so perfectly, and, as Flexner and I have shown, in addition to the soluble toxins there is an intracellular poison concerned in the production of the false membrane. Interesting investigations, which have greatly helped to elucidate the nature of these toxins, have been made on various similar vegetable and animal poisons, such as ricin and abrin from the former source and the venom of snakes, spiders and other poisonous animals.

The high hopes which were raised by the discovery of the soluble bacterial toxins that at last the way was opened for us to penetrate into the mysteries of the mode of action of pathogenic bacteria were soon doomed to disappointment, for similar powerful toxins, though diligently sought, could not be detected in the cultures of most other bacteria, and these among the most important ones, such as the tubercle bacillus, the typhoid bacillus, the cholera spirillum, the pneumococcus, the pyogenic micrococci. This disappointment was all the more acute because there was and is every ground for confidence that whenever we have in our possession a powerful toxin of this class, a strong protective antitoxic serum can readily be obtained.

Notwithstanding these negative results, the belief was not abandoned that bacteria harm the body mainly by poisoning, for it rests upon strong clinical and pathological evidence, as well as upon the study of the distribution of bacteria in the infected body. The search for poisons was turned from the fluid part of cultures to the bacteria themselves, and thus Pfeiffer succeeded in demonstrating as an integral constituent of the bodies of cholera spirilla toxic substances, which are liberated only when the bacteria degenerate or die. Intracellular poisons, which indeed previously, though of a different nature, had been extracted from bacteria by Buchner and by Koch, were subsequently found within typhoid bacilli and a number of other pathogenic bacteria.

It is of more than purely bacteriological interest to recognize the distinction between the small group of pathogenic bac-

teria, represented by the bacilli of tetanus, of diphtheria, and of botulism, characterized by the secretion of powerful soluble toxins, and the much larger group, containing most of the other pathogenic bacteria, which do not secrete similar strong toxins, for it is only the former which give rise to the production of antitoxic serum of marked protective and curative power.

The form of immunity resulting from injections or natural infections with the second class of bacteria belongs mainly to the bacteriolytic type, in which the complete antibody is not a single substance, like antitoxin, but is composed of two distinct elements, intermediary body and complement, of which only the former is produced or increased in the process of immunization. The bacteriolytic serums are also under suitable, but not readily controlled conditions, protective and curative, but owing, it would seem, mainly to the duplex nature of the antibody their successful therapeutic application meets difficulties which have not yet been overcome. The great practical problem of bacteriology to-day is to make available to medical practice the bacteriolytic serums such as antityphoid, antipneumococcus, antistreptococcus, antiplague, antidysentery serums. Such work as that of Marmorek, of Wassermann, of Neisser and Wechsberg, of Ainley Walker, upon the production, the properties, the conditions underlying the action of these serums is, therefore, highly important.

Our knowledge of the constitution and action of the intracellular bacterial poisons is most incomplete and at present cannot be applied in any very definite and satisfactory way to the explanation of the morbid phenomena of infectious diseases. Such investigations as those undertaken by Macfadyen and Rowland at the Jenner Institute of Preventive Medicine upon the expressed juices of bacterial cells promise to shed light upon this subject and in general upon the vital processes of bacteria. Of great value also are the recent researches of Vaughan upon intracellular bacterial poisons.

I find it difficult to reconcile myself to the doctrine that bacteria, such as the typhoid bacillus, the pneumococcus, and others of the class now under consideration, do their chief injury to the body, not while they are lively and vigorous, but after they become corpses and in consequence set free their protoplasmic poisons. Still this latter conception is the basis of a coherent hypothesis of infection, elaborated most fully recently by Radziewsky,* which rests upon a considerable amount of accurate observation and interesting experimental work. There can be no doubt that in the course of many infections there goes on an enormous destruction of the bacteria concerned so that the numbers of those indicated at any given time by microscopical examination and by cultures may represent only an insignificant fraction of the total progeny of the first invaders. I have been much interested in this phenomenon, since I became familiar with it over twelve years ago† in pneumococcus infections through the employment of a method which revealed in the exudates degenerating and dead pneumococci and their empty capsules in numbers often far exceeding the intact organisms; indeed, in some cases so many that they formed a large part of the exudate.

While all due weight should be given to such facts as these, the objections to the acceptance of the hypothesis just mentioned

* Radziewsky, *Zeitschrift für Hygiene*, 1900, XXXIV., p. 185, and 1901, XXXVII., p. 1.

† Welch, *Bulletin of the Johns Hopkins Hospital*, July, 1890, and December, 1892. Michaelis, *Berl. klin. Woch.*, 1902, No. 20, has recently reported the same findings.

as affording a complete explanation of the toxic phenomena of this class of infections are so obvious that naturally efforts have been made to learn whether bacteria which produce no strong soluble toxins in our ordinary culture media may not do so on other media of special composition or in a demonstrable way within the living body. Work in these two directions has not been altogether barren, as shown by results of experiments made by Hueppe, Cartwright Wood, Marmorek, and others along the former lines, and by Metchnikoff, Roux and Salimbeni along the latter, but it cannot be said that these experiments have led to any generally accepted solution of the main difficulties. Some are therefore inclined to lay the chief emphasis upon disordered cellular metabolism, but this is only a restatement of the question. Everybody recognizes abnormal metabolism as an essential condition in infections. The very point needing explanation is how the bacteria derange metabolism.

I wish here to advance a hypothesis which seems competent to explain the source, the mode of production and the nature of certain bacterial toxins. It would appear to be a natural inference from the receptor theory of Ehrlich and the recent work on cytotoxins. The following considerations will, I hope, make clear the essential points.

As I have already stated, we know that the injection of foreign cells, such as pathogenic bacteria, red blood corpuscles, spermatozoa, epithelium, into the tissues of a living animal leads to the formation of poisons, called cytotoxins, acting specifically upon these cells; that the substances which stimulate the cells of the host to produce one constituent of this class of toxins consist of certain atom complexes derived from the injected cells; that certain cells of the host thus stimulated generate and discharge one component of the toxin, called the intermediary body, which, although by itself not poisonous, becomes the medium of intoxication through union, on the one hand, with a preexistent toxophore substance, called the complement, and, on the other hand, with the foreign cell which started the reaction.

Such is the response on the part of the host to the entrance of the foreign cells; but how about a possible response of a like nature on the part of the invading cells toward the host resulting in the production of special cytotoxins, of analogous constitution, injurious to the host? This latter response, being of a vital nature, can take place only when the invading cells are living, as in the case of bacteria and other parasites.

I see no reason why suitable substances derived from the host may not stimulate parasitic organisms, through a physiological mechanism similar to that operative in the development of cytolytic immunity, to the production of intermediary bodies which, if provided with the requisite affinities, have the power to link complements to cellular constituents of the host, and thereby to poison the latter. Expressed in terms of Ehrlich's side-chain theory, certain substances of the host of cellular origin, assimilable by the parasites through the possession of haptophore groups with the proper affinities, become anchored to receptors of the parasitic cell, which, if not too much damaged, is thereby stimulated to the over-production of like receptors; these excessive receptors of the parasite, if cast off into the fluids or the cells of the host, there constitute intermediary bodies or amboceptors with special affinities for those cellular constituents or derivatives of the host which led to their production, and for others which possess in whole or in part identical receptors. Provided the host is supplied also with the appropriate complements, there result cyto-

toxins with special affinities for certain definite cells or substances of cellular origin in the host. The contribution of the parasitic cells to these cytotoxins is the amboceptors. Either the parasite or the host may provide the complements.*

It may perhaps aid in grasping the ideas here presented to imagine the bacterium, in the capacity of the host, as a structure so large that one could inject into it animal cells. Provided the proper receptor apparatus is present, the resulting reaction on the part of the bacterium, as described, would be a process of immunization against the animal cells through the formation of specific cellulicidal substances. In reality it is only certain atomic complexes of cells which are concerned in this immunizing reaction, and in comparison with these even the smallest bacterium is a gigantic object.

Looked at from the point of view of the bacterium as well as from that of the animal host, according to the hypothesis advanced the struggle between the bacteria and the body cells in infections may be conceived as an immunizing contest in which each participant is stimulated by its opponent to the production of cytotoxins hostile to the other, and thereby endeavors to make itself immune against its antagonists. These mutually antagonistic cytotoxins are capable of injuring the parasitic cells on the one hand or the body cells on the other, only when escaping combination outside of them they are anchored to the receptors of the cells to which their respective affinities are adjusted. This combination with the cells, if it does not result in too great injury to them, is the condition for further production of the cytotoxic intermediary bodies through over-production and discharge of receptors.* The im-

* We may thus speak of somatogenic cytotoxins resulting from the action of bacterial stimuli on cells of the host, and of bacteriogenic cytotoxins from somatogenic stimuli, also of somatogenic and bacteriogenic complements.

* It will be observed that these discharged receptors may be regarded as the equivalents of anti-immune bodies. E. W. Ainley Walker, in an interesting and suggestive paper on 'Immunization against Immune Serum' (*Journal of Pathology and Bacteriology,* March, 1902), shows experimentally that bacteria growing in immune serums produce anti-immune bodies, and thereby become more virulent. He concludes that 'the basis of bacterial virulence and of chemiotactic influence is identical, and constitutes that atom group which causes the production of the immune body.' My hypothesis includes the conceptions supported by Walker, and also much more. According to the hypothesis, certain bacterial anti-bodies are capable not only of neutralizing immune bodies of the host, but with the aid of complements also of poisoning the cells of the host. It is not difficult to imagine various conditions in which the anti-bodies of bacterial origin may escape neutralization before entering into union with the host's cells. The substances which stimulate bacteria to produce these antibodies need not necessarily be toxic to them; in, fact, toxicity, such as that of strong bactericides of cellular origin, would hinder their production. The essential things are that the stimulating substances have the requisite combining groups for bacterial receptors, and that the cast-off receptors be complemented within the body of the host. Each of the various bacteriogenic cytotoxins probably contains a multitude of partial amboceptors, with varying cytophilic and complementophilic affinities, in accordance with the views of Ehrlich and Morgenroth. It is self-evident that through a mechanism similar to that described parasites within the infected body may be stimulated by atom groups derived from the host to the production also of antibodies other than cytotoxins, such as various agglutinins, precipitins, antienzymes, and perhaps of uniceptors of the nature of secreted soluble toxins, or of enzymes, all adjusted against the host. Questions relating to the source and nature of the complements, particularly of intracellular complements, and also to anticomplements, are manifestly of importance in relation to the hypothesis, but it would complicate the subject too much to discuss these and other matters here, where my purpose is merely to outline the essential features of this new theory of infection with reference to the particular points under consideration.

portant factors determining the issue of the contest are the qualities, the relative proportions and the distribution of the bacterial and the host's cytotoxins.

The hypothesis thus outlined can be tested experimentally, but I regret that it has shaped itself in my mind so recently that I have not yet been able to make the desired experiments, which are, however, now started in my laboratory. Since my arrival here I am informed that these experiments have already furnished facts in its support, which will be published later.

Inasmuch as at least one component, and it may be both components, of the assumed bacterial cytotoxins preexist in the bacterial cells, it should be possible to demonstrate some of them in artificial cultures of bacteria, where they would be found especially as integral parts of the cells, unless extracted from the bodies of degenerating or dead bacteria. This corresponds with what is known concerning the situation of the poisons of the cholera spirillum, the typhoid bacillus and other bacteria characterized by the lack of strong soluble toxins. But the quantitative and other relations between these cultural cytotoxins and those produced in the manner described by the same bacteria during processes of infection are comparable to those between the normal antibodies and the immune antibodies. These relations would explain the familiar fact that cultures of bacteria of the class under consideration constitute in general only a partial and meager index of the toxic capacities of the same bacteria in the infected body. That cytolysins may, however, be present normally in large amount is illustrated by the hæmolysins of eel's serum and of snake venom.

In this theory, degenerated and dead bacteria, while recognized as a source of poisoning in infections, are not assigned an exclusive rôle in this regard. Living bacteria in the infected body, where they are under nutritive conditions not paralleled in artificial cultures, actively produce and secrete receptors which may become the means of intoxication of the body cells. From what has been said, we can comprehend how these diverse free receptors may enter into the formation of cytotoxins of the most varied and specific characters, such as erythrotoxins, leukotoxins, neurotoxins, nephrotoxins, spermotoxins, hepatotoxins, etc. Very probably in many instances these toxins are represented by so few receptors in bacterial cells in ordinary cultures that it would be hopeless to search for them there, although we may have convincing experimental and pathological evidence that within the animal body the same bacteria produce them abundantly under the stimulus of appropriate substances derived from cells of the host.

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(*To be concluded.*)

*THE LENGTH OF THE COLLEGE YEAR AND COURSE.**

A NUMBER of matters of general academic interest have occupied the attention of the university faculty, and to some extent that of the other faculties, during the year. The established policy of granting no honorary degrees was unanimously reaffirmed. The administration of the disciplinary authority of the university was devolved upon a committee consisting of the dean and four professors to be elected by the university faculty. The better conduct of examinations was much discussed; but owing to the difficulty experienced in discovering the sentiment of the students towards the so-called honor

* From the tenth annual report of President Schurman to the board of trustees of Cornell University.